REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, are respectfully requested.

By the present amendment, independent Claims 46, 49, 54, 57, 59, and 62 have been amended. Support for the phrase "suspending the vesicles for administration in a bulk solution, wherein the bulk solution has a pH which is physiologically benign" can be found at least at page 4, lines 15-19; page 6, lines 20-22, 28-29; and page 13, lines 6-10 of the specification (the latter of which defines "physiologically benign" as between pH 7 and about 7.8), and in original Claims 15 and 20. Support for "pharmaceutical preparation for administration *in vivo* to an animal" can be found at least at p. 4, ll. 12-13 of the specification and in original Claim 4. Claims 47, 50, 51, 53, 63 and 64 have been canceled without disclaimer or prejudice to that subject matter being pursued in a continuation or divisional application. No new matter is thus being added by this amendment. Moreover, these phrases were elements of Claims 50, 51, and 64, which have previously been examined, and thus the present amendments should require no further search.

Applicants would first like to thank Examiner Kishore for the courtesy of granting an interview to the undersigned and her colleague on May 13, 2003. During the interview, Applicants' representatives discussed possible amendments to the claims, to bring them into condition for allowance, as well as the possible submission of a declaration of an expert regarding the cited prior art. By the present submission, Applicants supply such a declaration, namely by Eric G. Mayhew, Ph.D. Applicants note that in an email received by the undersigned on June 20, 2003, the Examiner's supervisor, Thurman Page, indicated that

"subsequently submitted, and examiner requested Declarations are reasonable, and I will encourage the examiner to enter and consider." Applicants respectfully request that if the Examiner believes there are still outstanding issues with respect to the amended claims, that he contact the undersigned to discuss the same.

During the interview, Examiner Kishore indicated that his determination of patentability would have to be consistent with the Decision in Interference 103,469. Applicants respectfully submit that the claims involved in the interference differ from those currently pending. Likewise, the combination of prior art being argued in the interference likewise differs from that currently being applied. Finally, the Decision in Interference 103,469 was based on the Request for Adverse Judgment filed by Applicants in accordance with a settlement reached with the opposing party. No final Judgment by a three-member panel of the Board was ever entered, and therefore, it is believed that there is no Decision from the interference which is binding on the Examiner.

By way of background, Interference 103,469 was declared on October 11, 1994 between U.S. Application Serial No. 07/741,305, filed August 7, 1991 ("the Mehlhorn application")[1] and U.S. Application Serial No. 07/393,118, filed August 4, 1989 ("the Forssen application"). Mehlhorn was granted benefit of U.S. Application Serial Nos. 07/547,382 ("the '382 application"), filed July 3, 1990, 07/220,388, filed July 12, 1988, and 06/776,826, filed September 17, 1985. Forssen was granted benefit of U.S. Application

[1] The present application is a divisional of the Mehlhorn application in interference.

Serial No. 07/122,354, filed November 18, 1987. As such, Mehlhorn was designated Senior Party.

The Count in the interference reads as follows (as compared to current Claim 46):

Interference 103,469 Count[2]	Current Claim 46
A method of preparing a phospholipid-entrapped, cationic, lipophilic drug composition which comprises: a. forming liposomes in an aqueous medium containing an acid which has at east one ionizable functional group, is of sufficient polarity to be highly soluble in water and exhibits a low permeability through the vesicle membranes to give an acidic liposome-containing aqueous medium in which the acid is present in the internal and external liposome phases, said liposome being prepared from hydroxyamino (lower) aliphatic-substituted phosphatidyl carboxylic acid diesters of a tri-or higher functional aliphatic polyol in which the ester moieties are derived from a saturated or ethylenically unsaturated aliphatic monocarboxylic acid having at least 14 carbon atoms,	A method for preparing a pharmaceutical preparation for administration *in vivo* to an animal which comprises the steps of: (a) forming liposomes comprising a membrane in: (1) an aqueous medium containing an acid which is substantially impermeable through the vesicle to give an acidic liposome-containing aqueous medium in which the acid is present in the internal and external liposome phases; or (2) an aqueous medium containing a base which is substantially impermeable through the vesicle to give a basic liposome-containing aqueous medium in which the base is present in the internal and external liposome phases;
b. adding to the thus-obtained acidic liposome-containing aqueous medium a cationic, lipophilic drug, and	(b) adding: (1) to the thus-obtained acidic liposome-containing aqueous medium a permanently charged, chargeable, or pH titratable chemical species which is a cationic chemical species, or (2) to the thus-obtained basic liposome-containing aqueous medium a permanently charged, chargeable, or pH titratable chemical

[2] Claims 27-50 of the Mehlhorn application, which were designated as corresponding to the Count, are reproduced in Appendix A hereto.

	species which is an anionic chemical species; and
c. then adding a base whose cations cannot pass through the liposomes' lipid bilayers to charge neutralize the acid anions in the external aqueous phase, thereby inducing the cationic, lipophilic drug to pass into the liposomes' internal aqueous phase.	(c) adding to the external liposome phase: (1) a base to provide a pH gradient across the membrane of the liposome and thereby induce the cationic chemical species to pass into the liposomes' internal acidic aqueous phase, or (2) an acid to provide a pH gradient across the membrane of the liposome and thereby induce the anionic chemical species to pass into the liposomes' internal basic aqueous phase; wherein said cationic chemical species or said anionic chemical species is accumulated and entrapped within said liposome to produce a stable liposome vesicle-entrapped chemical species; and
	(d) suspending the vesicles for administration in a bulk solution, wherein the bulk solution has a pH which is physiologically benign.

During the interference, Forssen filed a Motion for Judgment (Appendix B) that Mehlhorn's claims were unpatentable over one or both of Nichols and Deamer, *Biochimica et Biophysica Acta*, 455:269-271 (1976)[3] and Cramer and Prestegard, Biochemical and

[3] This is not the Deamer reference presently applied, namely *Biochim. Biophys. Acta*, 274:323-335 (1972).

Biophysical Research Communications 75(2):295-301 (1977), optionally in combination with Fendler, *Liposomes in Biological Systems*, Gregoriadis and Allison, eds., 1980, pp. 87-100.

In a Decision on Preliminary Motions dated October 4, 1996 (Appendix C), Administrative Patent Judge ("APJ") Ronald H. Smith granted Forssen's Motion, and also noted that Forssen had admitted in its papers that its claims were unpatentable over the same reference. On May 14, 1998, Mehlhorn filed an Abandonment of Contest (Appendix D), pursuant to a settlement agreement between the parties. On May 19, 1998, a Decision by APJs Smith, Michael Sofocleous and Mary F. Downey, held that neither party was entitled to a patent containing claims in the interference. However, that Decision was not based on a review of the October 4, 1996 Decision by APJ Smith, but rather, was based on Mehlhorn's Abandonment of Contest. Thus, whether Forssen's Motion was sufficient or not was determined by a three-member panel of the Board.

Applicants also note that the Examiner has granted other patents to Applicants on related subject matter, namely 5,827,532, which issued from U.S. Application Serial No. 08/791,557, filed January 31, 1997, and 5,762,957, which issued from U.S. Application Serial No. 08/474,382, filed June 7, 1995, which is based on the same specification as the present application. U.S. Patent No. 5,622,713, allowed by another Examiner, issued from U.S. Application Serial No. 08/375,190, filed January 18, 1995, which is also based on the same specification as the present application.

The Examiner rejected Claims 46-54, 57 and 61-64 under 35 U.S.C. § 102(b) as allegedly being anticipated by Deamer et al. Alternatively, the Examiner rejected Claims

46-65 under 35 U.S.C. §103(a) as being allegedly obvious over Deamer et al. These rejections are respectfully traversed.

The primary focus of Deamer et al. is to analyze the effects of a pH gradient on fluorescent probes. Deamer et al. only uses liposomes to analyze the quenching effect on fluorescent probes in the presence a pH gradient. Deamer et al. does not disclose or suggest loading liposomes with drugs; nor does Deamer et al. disclose or suggest suspending the vesicles for administration in a bulk solution, wherein the bulk solution has a pH which is physiologically benign, as now required by independent Claims 46 and 52. (See ¶4 of Mayhew Declaration.) Thus, Deamer et al. does not anticipate the present claims.

In fact, Deamer et al. teaches away from suspending the vesicles for administration in a bulk solution having a pH which is physiologically benign (i.e., about pH 7.0-7.4). Deamer et al. analyzes the movement of a fluorescent probe into liposomes (fluorescence enhancement) at pH 5-9. Deamer et al. states at p. 326 that "the enhancement of atebrin fluorescence was maximal at pH 6.2 (ΔpH = 1.2), then decreased." Thus, in contrast to what was found by the present inventors, Deamer et al. teaches one of ordinary skill in the art to avoid a pH of 7-7.4 (physiologically benign) if one wants to maintain a concentration of a compound inside vesicles. (See ¶5 of Mayhew Declaration.) Therefore, Deamer et al. neither anticipates nor renders obvious the present claims. As such, withdrawal of this rejection is respectfully requested.

The Examiner rejected Claims 46-54, 59 and 61-64 under 35 U.S.C. § 102(b) as allegedly being anticipated by Cramer et al. or Kano et al. Alternatively, the Examiner

rejected Claims 46-65 under 35 U.S.C. §103(a) as being allegedly obvious over Cramer et. al. or Kano et al. These rejections are respectfully traversed.

Cramer et al. also teaches the physical chemistry involved in using a pH gradient to load certain simple ionizable molecules (fumaric and maleic acid) into a liposome. Cramer et al. does not disclose or suggest loading liposomes with drugs; nor does Cramer et al. disclose or suggest suspending the vesicles for administration in a bulk solution, wherein the bulk solution has a pH which is physiologically benign, as now required by independent Claims 46 and 52. (See ¶6 of Mayhew Declaration.) Thus, Cramer et al. does not anticipate the present claims.

Like Deamer et al., Cramer et al. actually teaches away from the present invention. Specifically, Cramer et al. initially suspends liposomes in a buffer of pH 7, and then adds acid to bring the pH down (i.e., away from a physiologically benign pH). Cramer et al. notes at page 298 that "adjusting the outside pH to a lower value (4.7 compared to 5.5) results in a rapid and greater accumulation of internal fumaric acid, followed by a slow simultaneous leakage of both acids." Like Deamer et al., Cramer et al. teaches that physiological pH is to be avoided if one wants to maintain a concentration of a compound inside vesicles. (See ¶8 of Mayhew Declaration.) Therefore, Cramer et al. neither anticipates nor renders obvious the present claims.

Kano et al. teaches the use of trisodium 8-hydroxy-1,3,6-pyrene-trisulfonate, pyranine, as a probe for monitoring the pH in the interiors of negatively charged liposomes and at the outer surface of positively charged liposomes. Kano et al. does not disclose or suggest loading liposomes with drugs; nor does Kano et al. disclose or suggest suspending the vesicles for

administration in a bulk solution, wherein the bulk solution has a pH which is physiologically benign, as now required by independent Claims 46 and 52. (See ¶9 of Mayhew Declaration.) Thus, Kano et al. does not anticipate the present claims.

Like Deamer et al. and Cramer et al., Kano et al. actually teaches away from the present invention. Specifically, Kano et al. states at p. 298 that pH gradients are not maintained when liposomes are transferred from ph 10.00 to pH 7.12 (physiologically benign pH). Kano et al. further states that "pH gradients can be maintained in transferring liposomes from pH 7.00 to pH 2.00 or pH 9.87." Like Deamer et al. and Cramer et al., Kano et al. teaches that physiological pH is to be avoided if one wants to maintain a concentration of a compound inside vesicles. (See ¶10 of Mayhew Declaration.) Therefore, Kano et al. neither anticipates nor renders obvious the present claims.

Withdrawal of this rejection is therefore respectfully requested.

Further and favorable action in the form of a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this Amendment, or the application in general, prior to the requested personal interview, it would be appreciated if the Examiner would contact the undersigned attorney by telephone so that prosecution is expedited. In any event, the undersigned awaits being contacted for the requested personal interview.

Respectfully submitted,

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